BLA 125197 Resubmission
CMC Review of Complete Response letter items (including 483 items) and additional information not contained in original submission

sipuleucel-T (Provenge®)

Dendreon Corporation

Division of Cell and Gene Therapies
Office of Cellular, Tissue, and Gene Therapies

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EXECUTIVE SUMMARY

Recommendation: The CMC review team agrees that Dendreon has provided adequate data to address the CMC concerns from the FDA Complete Reponse (CR) letter dated May 8, 2007. We recommend that a license for sipuleucel-T (Provenge®) be granted.

This memo focuses on review of Dendreon's responses to the outstanding CMC concerns, the second pre-licensure inspection, and product labeling. Dendreon was issued a Complete Response letter on 5/8/2007 that included 7 CMC issues, including unresolved inspectional observations listed on Form 483 (483 items). The complete response to these issues was provided in amendment 34 (BLA resubmission) which extensively references individual amendments 9 through 33 and communications between the FDA and the sponsor that occurred in the three year interim. Additional Requests for Information were made during the review period and the responses were provided in Amendments 34-48 and additional communications. This information was reviewed and the response to CR letter items 1-7 are considered adequate.

Two inspections of the Dendreon manufacturing facility in New Jersey were conducted on February 2007 and January 2010. All of the pre-license inspection-related issues from the CR letter have been adequately resolved. The second inspection confirmed that the sponsor has implemented the required changes to their manufacturing and product testing and tracking procedures. Due to the complex logistical nature of the manufacturing process of this autologous product in coordination with shipping times and patient scheduling it is important to demonstrate that the entire process was built around operating parameters that ensure product quality from the point of cell collection through delivery of product for infusion. The sponsor has justified the underlying assumptions in the manufacturing process and provided data demonstrating their ability to manufacture quality product.

The proposed product labeling has been reviewed and revised to reflect the product more accurately. The recombinant antigen PAP-GMCSF (PA2024) is listed as an active ingredient. Changes were made to the proposed shipping container labeling to be in compliance with the regulations.

Reasons for issuing CR letter comments after review of the original submission

On May 8, 2007 the sponsor was issued a CR letter that included seven product related items. These included both inspection items that were not adequately resolved in the sponsor's response to the presented 483 items, and CMC issues uncovered during the BLA original submission review. The areas of concerns were improper product sample tracking within the QC lab; inadequate process validation within the cGMP modules; inadequate demonstration of sterility method equivalence; and inadequate assay validation, insufficient demonstration of adequate product shipping conditions, a lack of demonstration that the product can be distributed as intended, and questions surrounding apheresis stability.

May 2007 CR letter CMC comments to Dendreon:

1. Outstanding issues from your pre-license inspection, dated February 12-16, 2007, have yet to be resolved.

2. The stability of the --b(4)---------- and the potential effect on sipuleucel-T cannot be fully evaluated from the data provided. It is not clear that the data presented in Figure 8 in section 3.2.P.2.3 are representative of the range of clinical experience. Please provide a more detailed explanation of how the stability studies of the -b(4)- were conducted.

3. Additional data are needed to validate shipping of sipuleucel-T during elevated external temperature conditions. Please provide data verifying that sipuleucel-T product attains the specified 2-8°C temperature range within a defined time period and maintains this temperature throughout the remainder of the shipment when exposed to high external temperature shipping conditions. Please provide data showing that product quality is maintained within the limits of the acceptable ranges of temperature and time. These data should be generated from studies conducted at the New Jersey facility.

4. To support the shipping validation studies addressed in item 3, please address the following:

    a. Please establish a maximum process step time for formulation of the sipuleucel-T product in lactated Ringer's solution before packaging in the shipping container with the gel packs.

    b. Please submit data demonstrating that you can ship sipuleucel-T from the New Jersey facility and infuse it into the patient within the 18 hour shelf life. We recommend that you submit data from all clinical lots manufactured at the New Jersey facility. The data should include the destination and the time from formulation to infusion.

5. Your comparability analysis included data from product manufactured at the Seattle and New Jersey facilities. Please provide additional data from the other manufacturing sites that produced clinical product for the Phase 3 clinical trials. Please provide information on the number of lots manufactured at each manufacturing site.

6. Additional information is needed to assess the validation of the -b(4)------- method as an alternative sterility test method. Please address the following:

    a. For each of the datasets provided, please clarify where and when the studies were performed and the -b(4)-- model that was used. We note that the -b(4)---------- ------- is used in Seattle and the --b(4)---------- is used in New Jersey. Please discuss the differences in the-b(4)- systems, including any differences in the --b(4)----------. If this information is contained in another regulatory file you may submit a letter of cross-reference obtained from the manufacturer authorizing the Agency to refer to information contained in such file.

b. We note that you plan to "further demonstrate the suitability of the --b(4)----------.” Please submit data from these additional studies.

c. If you intend to use the --b(4)----------, please submit data to demonstrate that the -b(4)-------- formulation does not have any bacteriostatic and fungistatic effects in this method.

7. Additional data or justifications are needed to support your analytical method validations. Please address the following:

a. We note that both the --b(4)---------- methods are tested in --b(4)----------. For each of these assays, please establish a maximum variability between results of -b(4)---- samples. Please describe what procedures will be followed if the maximum variability is exceeded.

b. We note that only gram positive organisms are used for the validation of the gram stain assay. Please include gram negative organisms as part of the validation.

c. Please revalidate your --b(4)---------- method for accuracy and intermediate precision. Please include precision studies that demonstrate the ability of operators to differentiate between viable and non-viable cells.

Regulatory activity since original BLA submission: BLA Amendments 11-33 were submitted prior to the BLA resubmission. The BLA resubmission was provided in Amendment 34. BLA amendments 35-48 were provided as supplemental information and as responses to FDA requests for information to clarify points from the BLA resubmission. The BLA resubmission extensively referred to BLA Amendments 9-27, but Amendments 30-48 were also relevant. A second pre-license inspection was conducted Jan 25-29, 2010 and many review items were clarified during inspection. Additional information and data was provided in emails received during the review period that were subsequently submitted as BLA amendments. The sponsor also provided a physical copy of the final product primary container and photographs of the package shipping configuration. The BLA original submission and Amendments 1 – 32 were submitted in CTD format and the BLA resubmission and Amendments 33-48 in the eCTD format.

PRODUCT DESIGNATIONS :

Active ingredients:

Sipuleucel-T is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer. Sipuleucel-T consists of autologous peripheral blood mononuclear cells, including antigen presenting cells (APCs), that have been activated during a defined culture period with a human recombinant protein, PAP-GM-CSF, consisting of prostatic acid phosphatase (PAP), an antigen expressed in prostate cancer tissue, linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune cell activator. The active ingredients are autologous antigen presenting cells and PAP-GM-CSF.

PA2024 is synonymous with PAP-GM-CSF. PA2024 is the sponsor's internal term for the recombinant protein. In the package insert and other labeling the protein is designated PAP-GM-CSF. The protein ----b(4)----------
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To manufacture sipuleucel-T, a patient's cells are collected by leukapheresis approximately 3 days prior to the infusion date. Red blood cells and granulocytes in the leukapheresis product are reduced by two buoyant density gradient separations, retaining the populations of leukocytes. PAP-GM-CSF is then added to the cells. During culture, PAP-GM-CSF can bind to and be processed by antigen presenting cells into smaller protein fragments. ----b(4)----------
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The cells are cultured in the presence of PAP-GM-CSF for 36-44 hours. After culture, the cells are washed and suspended in lactated ringer's solution for the final formulation of sipuleucel-T,

and shipped to the infusion site for infusion into the patient. Minimal residual levels of the intact PAP-GM-CSF are detectable in sipuleucel-T.

Nomenclature for Sipuleucel-T

Trade name	Provenge®
United States Adopted Name (USAN)	sipuleucel-T
NDC code assignment	NDC30237-8900-6
UNI code assigments	**sipuleucel-T:** 8Q622VDR18
	PAP-GM-CSF: N5E5Q8249O

Table of Contents for CMC Review

SECTION I: REVIEW OF COMPLETE RESPONSES TO MAY 7, 2007 COMPLETE RESPONSE LETTER (CMC)

CR ITEM #1. Outstanding issues from your pre-license inspection, dated February 12-16, 2007, have yet to be resolved.

A pre-license inspection (PLI) of Dendreon Corporation, US License # 1749, Morris Plains, New Jersey, was performed on February 12 – 16, 2007 by CBER and the Office of Regulatory Affairs, New Jersey District Office. A Form FDA 483 was issued to the firm at the close out meeting on February 16, 2007. A total of nine inspectional observations were made.

483 item 1. There are no data to support the concurrent manufacturing of b(4) lots within a clean room module. Process Validation Report QVD No. 50999 includes data from only one day of concurrent manufacturing of -b(4)--- lots in Module -b(4)----- lots from a second day. The commercial process as described in the Biologics License Application (BLA) specifies the use of b(4) clean room modules, total of b(4) workstations,b(4) lot per station.

Summary of sponsor's response: Dendreon referred to the following table to provide supporting documentation, which included meeting minutes.

Amendment Number	Date	Topics
032	July 30, 2009	Information requested by FDA at Type C meeting held June 5, 2009: • Summary of validation of LIMS
024	Oct. 22, 2008	Information requested by FDA at Type C meeting held October 16, 2007 (refer to FDA meeting minutes): • QC sample management using LIMS • Manufacturing capacity qualification study (b(4) workstations) • Campaign manufacturing • Copy of Dendreon's response to Form 483 (March 2, 2007
015	Sep. 14, 2007	• Manufacturing capacity study (b(4) workstations)
009	April 20, 2007	Information requested following the response to Form 483 (March 2, 2007) • QC sample management • Process step alert limits

Review of supporting documentation: Supportive information was found in each referenced documents.

In amendment 24 Dendreon provided the results from a validation study which was meant to be the complete response to this inspection issue. The design of this study took into account recommendations made by CBER. **OCBQ and DCGT reviewed the results from the b(4) workstation process validation study and found that it was adequate.**

This study used healthy donors as the cell source, and therefore the final product was not shipped back to the infusion site for patient infusion. For this study b(4) individual lots were all processed for Dayb(4) manufacturing within a -b(4)- time window.The processing of b(4) Day b(4)lots and b(4) day b(4) lots within a -b(4)- time frame equals the proposed maximum lot production capacity. The maximum proposed production level is b(4)Day b(4)lots and b(4)Day b(4) lots using b(4) modules and -b(4)--- cGMP work shifts.

The sponsor provided a graphical representation of the overall manufacturing schedule. On November 13, 2007,b(4) Day b(4) lots were processed, with processing occurring in b(4) of b(4) lots. The --b(4)----------. Within each group the processing of individual lots was timed about -b(4)--- apart. During processing of the second group of Day b(4)lots, Day b(4)processing was performed on b(4)additional lots. Approximately b(4)---- separated the processing of these b(4) types of intermediates in the -b(4)--workstation. It is not indicated if these processing times include changeover procedures. All manufacturing steps (including final product packaging) and QC testing steps were performed for each lot.

All day b(4) processing was initiated at regular -b(4)- intervals. Commercial manufacturing would not be timed as such, and to that extent this study does not represent a worst case scenario, but the study design is a reasonable test of their manufacturing process. The overall design did incorporate the two major elements the Agency requested: 1) processing in all b(4) workstations on the same day, and b(4) an overlap in the processing between Day b(4) and Day b(4) product intermediates. All b(4) lots were processed for this study. The processing of b(4) lots represents half of the intended commercial throughput, but since the total processing time spanned roughly -b(4)--- and the sponsor will have -b(4)---------- manufacturing shifts the number of lots processed for this validation study is adequate.

There were 3 manufacturing incidents that took place during this study:

- Lot -b(4)--: was found to have an excessive ---b(4)----------.

- Lot # -b(4)--: was found to have a low -b(4)--- and $CD54^+$ result during manufacturing and as a consequence Day b(4) Manufacturing steps and QC testing were not performed. Dendreon attributed this to the patient apheresis material. Dendreon compensated by using an additional production lot (-b(4)--) that was initiated as a replacement for b(4) processing.

- Lot # -b(4)--- Day: the culture volume was miscalculated as a consequence of operator/verifier error. The lot was discontinued after the b(4) processing and so Day b(4) manufacturing steps and QC testing were therefore not performed. The sponsor attributes the root cause to the incoming patient apheresis unit, but did not elaborate on what this meant.

An additional production lot (-b(4)-) was initiated as a replacement for the concurrent b(4) processing which was completed without problem. Dendreon thus believes the incident had no impact on the qualification study. The review team agrees.

As part of this study Dendreon also performed environmental monitoring and all testing passed for both processing areas and personnel.

This study adequately addressed the sponsor's ability to manufacture using all b(4) **workstations in** b(4) **cGMP modules and to complete all QC testing as required.** For a discussion of manufacturing logitics including product shipping see Section II.A.

483 item 2. Insufficient personnel from the New Jersey manufacturing site were available to perform Aseptic Process Validation in Module b(4) (QVD No. 51000). A New Jersey contract employee with no previous training in aseptic operations gowned in to participate in the aseptic simulation to support this validation study.

Sponsor response (summary): A new aseptic process validation study was completed in 2007, with staff fully trained on NJ procedures, and reported in Amendment 24. Results from this validation study were considered adequate. Regarding the NJ contract employee cited in this 483 item, Dendreon clarified that his curriculum vitae confirmed his prior aseptic experience and he was trained per SOP 11034, "New Jersey IMF Gowning Procedure", prior to entering the clean room (training completed on August 28, 2006). This contract employee did not perform any process simulation during the validation study, and his role was to simulate a visitor as allowed by SOP 11034. A copy of the training record for this employee was attached. **The response was considered adequate.**

483 item 3. The quality control laboratory did not demonstrate adequate ability to maintain the chain of identity for the autologous product.

a. No documented system is in place to track and manage the flow of the samples. There is also an inconsistent labeling system to maintain the chain of identity of the samples.

b. The commercial system, as described in the BLA and presented during inspection, specifies the use of a bar code to maintain identity. The QC laboratory does not have the capacity to read the barcode, nor is it connected to the -b(4)- database used throughout the rest of manufacturing. In addition, information sent from the QC laboratory to the manufacturing module does not contain a bar code.

Sponsor response (summary): Dendreon addressed these two issues on several levels and ultimately through the same mechanism**:** Laboratory Information Management Systems (LIMS) software was customized to Dendreon's needs and implemented in the QC lab as a sample tracking and data entry system, and barcode scanners were placed at each analyst workstation along with another barcode reader for use in conjunction with the -b(4)- system to transmit intermediate test results directly to the cGMP manufacturing area. The use of LIMS within the QC lab and in dedicated areas within the Morris Plains, NJ facility was observed during the Jan 2010 pre-license inspection. The inspection provided a clearer picture of how LIMS is actually used. The flow of personnel and samples was also greatly improved from the system used at the time of the 2007 pre-license inspection.

LIMS has the built in capability to track all samples. By nature of scanning all samples that come into the lab at each specific analyst workstation LIMS would know which samples are in the QC at any given time and which assays are either in process or complete. It is possible within LIMS to scroll down and click through various pull-down lists to be able to tell what has and has not been completed. LIMS can be accessed at any LIMS workstation within the QC lab. The QC supervisors can even access it offsite using -b(4)- software and the appropriate passwords and login accounts.

<u>Barcode scanning</u>: An -b(4)--generated barcode and human readable label are present on forms FRM-60178, (sample submission) and on the -b(4)-------- report page. All sample tubes also have a barcode label.

In amendments 24 and 32 Dendreon provided a description of LIMS and how it is used in the QC lab. Dendreon provided a diagram of how products are tracked in the QC lab beginning with sample submission in the QC lab. --b(4)---
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the QC lab. The sponsor has clearly taken extensive measures to respond to the Agency's concern about the QC laboratory. In addressing this issue they have installed new equipment, new software, revised SOPs, and established new procedures. These new measures should be capable of handling product sample testing.

483 item 4. During Day b(4) processing on Tuesday, February 13, 2007, we observed that lot number -b(4)-- being processed at step --b(4)in workstation b(4)was resuspended in -b(4)----------before being placed in the----------b(4)----------. According to Technical Report 30366, the validated time for holding---b(4)----------

Sponsor response (summary): A review of the study that led to TR 30366 showed that a --b(4)----------used, and the data therefore support establishing a process step time for this stage of manufacturing as --b(4)--------, with no impact to product quality.

Concerning Dendreon's ability to ensure proper production management and timing, the Agency relayed the following comments during a telecon between CBER and the firm dated April 4, 2007:

- Please establish time limits for individual process steps during manufacturing.
- Please describe procedures for avoiding a bottleneck at critical equipment in the QC lab (i.e. --b(4)---------- analysis, secondary equipment in case of equipment failure for equipment that is not duplicated).
- Please establish time limits for sample holding in the QC lab and provide justification for holding conditions.
- Please discuss the potential bottleneck in the pass-through areas. Please discuss the ability to transfer information electronically.
- Please describe the mechanisms for managing logistical oversight, particularly in regard to sample processing in the QC lab.

Dendreon has submitted the requested information. **The response was considered adequate.** Dendreon also informed the agency that they are considering electronic batch records in the future.

483 item 5. SOPs 11058, Exception Reporting, and 11059, Investigations, contain no time frame for closing out reports.

Sponsor response (summary): SOP 11058 and 11059 will be revised to specify that Exception Reports and Investigations must be completed within 30 days. Extension beyond 30 days may be granted upon acceptable justification being provided and approved by management and QA. The revised SOPs were submitted as an amendment, which were subsequently reviewed. **The response was considered adequate.**

483 item 6. Regarding SOP 10839, Change Control:

a. There is no review of the Change Control Regulatory Impact Assessment (Form 60042) by the Regulatory Affairs group.

b. *Form 60042 is used to document the Change Control Review Board (CCRB) decisions but this is not stated in the SOP.*

Sponsor response (summary): SOP 10839 was revised to provide clarity that the Regulatory Affairs (RA) department reviews all changes by completing a Regulatory Impact Assessment prior to CCRB approval in addition to serving as CCRB signature for approval. The revised SOP 10839 defines the responsibilities of RA as related to valuation of reporting requirements, and all affected staff will be trained on the revised procedure. The revised SOP 10839 was submitted as an amendment and was subsequently reviewed. The revised SOP 10839 will include emphasis that the Regulatory Submission section of FRM 60042 correctly represents the regulatory submission requirements identified on completed FRM 60005, "Regulatory Impact Assessment", to ensure consistency in the regulatory assessment on both forms. **The response was considered adequate.**

483 item 7. Regarding SOP 10047, Supplier, Contractor, and Vendor Audits:

a. *An audit team is defined as including a "qualified auditor," however, there is no stipulation as to what qualification for auditing would entail.*

b. *It is actual practice that the audit report would be reviewed by Quality Systems personnel but this is not stated in the SOP.*

Sponsor response (summary): Dendreon will revise SOP 10047, "Supplier, contractor and Vendor Audits", to include the proficiency requirements necessary for auditor qualification. Revision will be completed and implemented by March 15, 2007. The SOP will be modified to require review and approval of all supplier, contractor and vendor audit reports by Quality Systems management prior to final approval and distribution. **The response was considered adequate.**

483 item 8. There is no documentation to support the formulas used in the --b(4)----- spreadsheets, -b(4)----------Results, and In Process and Final Product --b(4)----- Results, used to generate sample analysis results.

Sponsor response (summary): SOP 11155, "Design and Qualification of -b(4)- Spreadsheets" was to be implemented to specify requirements for documenting the verification of formulas used in -b(4)---------- spreadsheets. The formulas for calculation of -b(4)---------- ---------- Results, and In Process and Final Product --b(4)---------- Results will be qualified and documented. **The response was considered adequate.**

Note: This SOP is no longer relevant as -b(4)-- is no longer used in the QC lab. LIMS software has replaced the QCWS spreadsheets that were used to perform the calculations and LIMS now performs the calculations and the results are sent electronically to the GMP suite. In an email received on 3/9/2010 the sponsor provided a summary table documenting all critical calculations that are performed in the making of sipuleucel-T (see Section II D: Software Used in the Making of sipuleucel-T).

A consult reviewer for LIMS software concluded the validation is acceptable (see Section III Appendix C: Consult Review Memos for Software Validation)

483 item 9. There is no documentation that Senior Manufacturing Associate b(6) has received cGMP training.

Sponsor response (summary): Dendreon clarified the training the individual in question received and stated they will audit all employee training records. All new personnel will be required to receive GMP 101 training. **The response was considered adequate.**

Summary of response to CR letter item #1. Responses provided by the sponsor in the official 483 response adequately addressed inspectional items 2, 4, 5, 6, 7, 8, and 9. Inspection items 1 and 3 were adequately addressed by information provided in subsequent telecons and BLA amendments 9 through 32. As such the sponsor has adequately responded to all 9 inspection related CMC items and **the response to CR letter item #1 can be considered adequate.**

CR ITEM #2: The stability of the --b(4)---------- and the potential effect on sipuleucel-T cannot be fully evaluated from the data provided. It is not clear that the data presented in Figure 8 in section 3.2.P.2.3 are representative of the range of clinical experience. Please provide a more detailed explanation of how the stability studies of the b(4) were conducted.

Summary of sponsor's response: Dendreon referred to BLA Amendment 17.

Review of supporting documentation: Dendreon responded to this item by providing the requested information. The data show that the lots used in the b(4) stability study are representative of the types of lots typically generated for clinical use.

In amendment 17 Dendreon provided extensive summary information on the b(4) development product lots used in the b(4) stability studies along with the same summary information for b(4) lots from the D9902B trial. Line listings were also provided for all b(4) lots. A comparison of potency data (# of $CD54^+$ cells in the final product and the level of CD54 upregulation) was also made with product lots from D9901, D9902A, D9902B, and P-11 trials. The summary statistics on these data sets were all comparable and the range of product lots produced was quite similar.

[b(4)]

Our own analysis of select product parameters comparing the b(4) developmental lots used in the b(4) stability study with cumulative data compiled from all of their clinical studies suggests a similar trend. Though Dendreon did not always measure the same product attributes for every clinical study or for every lot, where data is available it suggests that the -b(4)- source material that happened to be used in the b(4) study was not superior to any significant extent than what was typically observed in patient lots generated in D9901, D9902A, D9902B, or P-11. The average number of --b(4)---------- present in the b(4) was on average remarkably consistent, although the minimum number of cells was higher in the developmental lots.

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CR ITEM #3: Additional data are needed to validate shipping of sipuleucel-T during elevated external temperature conditions. Please provide data verifying that sipuleucel-T product attains the specified 2-8°C temperature range within a defined time period and maintains this temperature throughout the remainder of the shipment when exposed to high external temperature shipping conditions. Please provide data showing that product quality is maintained within the limits of the acceptable ranges of temperature and time. These data should be generated from studies conducted at the New Jersey facility.

Summary of sponsor's response: Dendreon referred to the following table for the location of supporting documentation, which included meeting minutes. Supportive information was found in Amendment 32 which provided the results from a study described in Amendment 24.

Table 2 BLA Amendments Related to Item 3

Amendment Number	Date	Topics
032	July 30, 2009	Information requested by FDA at Type C meeting held June 5, 2009: • Results from -b(4)----- temperature mapping study (protocol provided in Amendment 024)
027	Apr. 16, 2009	• Dendreon meeting minutes for January 15, 2009 teleconference
024	Oct. 22, 2008	Response to Item 3, with reference to FDA meeting minutes dated November 15, 2007: • Temperature mapping study design • Comparison of sipuleucel-T and simulated product

This item was included in the May 2007 CR letter because the study design and outcome data from the original submission were considered inadequate for several reasons:

- When examined in their totality the shipping validation and shipping container validation studies involved little shipment of actual product or simulated product. Dendreon put a lot of emphasis on the --b(4)-------- data because they believed it represented robust testing conditions for temperature extremes and durations that would exceed anything the commercial product would likely encounter. Few shipments of actual product were performed in support of shipping validation. The BLA review team therefore placed a lot of scrutiny on the design of the -b(4)---- tests. It was questionable whether the design parameters accurately reflected what a real shipment would be exposed to during temperature extremes of summer and winter, especially considering all the different routes and combinations of air and ground transportation. The shelf life of the product is set at 18 hours, and the sponsor's protocols allow any amount of that time to be spent sitting at the facility, en route to the infusion site, or sitting at the infusion site.

- Limited information had been provided on the intended shipping routes and times. Both summer and winter profiles were designed into the previous study. However, upon examination it appeared that the design had not adequately incorporated Dendreon's extensive shipping experience under IND and the complex shipping logistics and lengthy routes that would be part of shipping commercial product.

- A comparison of the --b(4)---------- data and the shipping study data using simulated product in the commercial shipping container showed --b(4)---------- ----------. This raised the question of whether the --b(4)---------- truly represented the worst case scenario.

- None of the shipments (using simulated product) were sent from the NJ facility. The NJ facility was the receiving end.

- The -b(4)---------- studies just barely passed in one case and no attempt was made to repeat the study.

To respond to this CR item Dendreon conducted a temperature mapping study where the sponsor shipped similated product in the same shipping container as will be used commercially to b(4) destination cities. The shipments were conducted over a period of -b(4)- and destinations and times through the calendar year were meant to reflect summer and winter profiles. Simulated product originating from the New Jersey facility was shipped with temperature data collected from the outside of the shipping container, as well as from inside the product bag using data loggers.

Dendreon concluded that the results of this -b(4)--long study demonstrate that:

- The -b(4)---------- profiles used to validate the sipuleucel-T shipping container exceed the-b(4)--- stresses that were measured in the -b(4)--long study.
- Product shipped in the validated shipping container attains the specified 2-8°C temperature range within an acceptable period.
- The required product temperature is maintained under shipping conditions that cover extremes of both high and low external conditions as defined in the validation of the shipping configuration.
- The shipper had very consistent performance whether under extreme temperature stress or mild shipping conditions. Product temperatures were slightly colder during the winter half of the study, however all products were well within the 2-8°C specification upon arrival.

I agree with these conclusions. The results from this study adequately address CR letter item #3

The study was meant to establish that both the summer and winter profiles used to validate the shipping container are representative of the temperatures encountered in distribution and that both profiles exceed the thermal stresses that were measured in the -b(4)--long study. The study was also conducted to demonstrate the ability of the shipping container and its gel packs to

properly cool the final product after --b(4)---------- formulation and maintaining product temperature once it is within 2-8°C. Simulated product was used to allow for placing the temperature data loggers inside the product bag. Attaching data loggers to the outside of the bag inside the container would not provide an accurate measure of product temperature.

During the October 16, 2007 teleconference the Agency asked Dendreon about the comparability of simulated to the final product. --b(4)---------- ----------
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Summary of shipping container validation study: The design of this new validation study far surpasses what was conducted previously and addresses our concerns about the design and execution of the previous studies not accurately reflecting what the commercial product would be exposed to when shipped throughout the country throughout the year. The number of target cities and the total number of shipments was robust and provides valuable information on the varied temperature profiles to each location and between different shipments to the same locations. The --b(4)--------- design does expose the product to an overall greater amount of extended temperature, yet the product ramp-down cooling times were actually longer with actual shipments. The data set generated from these studies is quite valuable and show that the shipping container performed as needed to relevant geographic sites at representative times per year. **The response to this issue can be considered resolved.**

CR ITEM #4. To support the shipping validation studies addressed in item 3, please address the following:

a. Please establish a maximum process step time for formulation of the sipuleucel T product in lactated Ringer's solution before packaging in the shipping container with the gel packs.

b. Please submit data demonstrating that you can ship sipuleucel-T from the New Jersey facility and infuse it into the patient within the 18 hour shelf life. We recommend that you submit data from all clinical lots manufactured at the New Jersey facility. The data should include the destination and the time from formulation to infusion.

Summary of sponsor's response: Dendreon referred to Amendment 24 to provide the supporting information for CR item 4a, and to the following table for CR item 4b.

Table 3 BLA Amendments Related to Item 4b

Amendment Number	Date	Topics
032	July 30, 2009	Information requested by FDA at Type C meeting held June 5, 2009: • Transportation and logistics data for all D9902B lots manufactured in the New Jersey facility
024	Oct. 22, 2008	Response to Item 4b, with reference to questions from FDA meeting minutes dated November 15, 2007
016	Nov. 5, 2007	• Transportation and logistics data for clinical lots manufactured in the New Jersey facility
015	Sep. 14, 2007	• Transportation description • Shipping logistics model

Review of supporting documentation: Supporting data to CR item 4A was elapsed time data collected during the b(4) workstation process capacity validation study that justifies their choice of establishing a -b(4)--- step time; and data from a --b(4)---------- stability study that shows the product is stable for --b(4)----------. The final product is resuspended in ----b(4)---------- it is packaged with cold gel packs prior to shipment. A second stability study was performed by the sponsor using a combination of --b(4)---------- and shipping container cooling steps to more accurately simulate the temperature conditions the product would be exposed to during packaging and shipping.

Supporting data for item 4B comes from several studies and from information gathered on inspection:

- Proposed shipping routes and times and estimated delivery times that document that using proposed planned routes and times will allow delivery of the product within the logistical constraints they must adhere to, such as delivery during normal business hours (for a discussion of logistics see Section IIA: Manufacturing Logistics)
- Shipments of final product to various destinations on the east coast and -b(4)--
- Shipments of final product to --b(4)---------- and Seattle from the Morris Plains, NJ facility (data provided on inspection at FDA request).
- Shipment of b(4) lots produced during the second pre-license inspecton to Seattle

The cumulative data from all these studies resolves the concerns raised in CR item 4.

Review of Item 4A:

The justification for a time period of -b(4)---- was provided in Amendment 24. The sponsor used data collected in the b(4)workstation process validation study to derive the necessary time
---b(4)--- ----------

---b(4)--- ----------

---b(4)--- ----------

---b(4)--- ----------

The data summarized in the table below demonstrate that the product is stable for 3 hours at room temperature for all the parameters measured.

[b(4)]

After review of this information it is clear that -b(4)---- is appropriate step time. The specified time range is logical based on their observations from the b(4) workstation process validation study and the room temperature stability data support product stability for that length of time before it is packaged. **The response to CR Item 4A is adequate.**

Response to Item 4B:
Note: sipuleucel-T has a dating period of 18 hrs, and infusion must begin with the 18 hrs.

Supporting data for item 4B can be found in the following 4 pieces of evidence:

- Proposed shipping routes and times and estimated delivery times that document that using proposed planned routes and times will allow delivery of the product within the logistical constraints they must adhere to, such as delivery during normal business hours (for a discussion of logistics see Section IIA: Manufacturing Logistics)

Dendreon provided two tables: one showing b(4) apheresis collection cities from around the country (representing different geographical regions), and another table showing the predicted return route travel times. For some cities only a single route was shown and for others three. For some cities travel times for both an all ground route and an air/ground combination were presented. The sponsor did not calculate the elapsed times between these steps, but the overall timing is consistent with being able to deliver the product before product expiration. The elapsed time to delivery of the final product was typically during normal business hours of apheresis sites and infusion sites Dendreon (--b(4)--------- in all cases).

The sponsor did not provide actual shipment data on the same target cities, but did provide data on approximately -b(4)- lots distributed to b(4) cities. The most distant target locations were --b(4)----------. The sponsor estimated at least b(4) hours of remaining expiry for shipment of final product to these cities and the final product shipping data confirmed these estimations..

Other locations had up to b(4) hours estimated remaining expiry. For many destinations the amount of estimated remaining expiry was around b(4) hours. Delivery times did not correlate with distance from the manufacturing site.

This data is consistent with clinical data provided in Amendment 42 in response to a request for information from the clinical reviewers about the start of infusion time for product manufactured during clinical trials. That data showed the mean start time of infusion was -b(4)---- hours of expiry used (-b(4)- hours of expiry remaining). For 90% of product lots infusion began with b(4) hours of expiry remaining. **The proposed shipping times and routes support their ability to deliver the product as needed for commercial distribution.**

Summary of data in support of CR Item 4B: The data from the studies conducted by Dendreon demonstrate the ability to ship to a wide range of destinations and deliver not only within the 18 hour shelf life, but to be able to do so with a reasonable time left for product handling at the infusion sites such that product handling and initiation of product infusions would not be rushed. Data provided on apheresis shipments also support shipment routes and times consistent to what will be needed for commercial manufacturing. Cumulatively, these data resolved the issues raised in CR item 4 and **the response is adequate.**

CR ITEM #5: Your comparability analysis included data from product manufactured at the Seattle and New Jersey facilities. Please provide additional data from the other manufacturing sites that produced clinical product for the Phase 3 clinical trials. Please provide information on the number of lots manufactured at each manufacturing site.

> Sponsor's official response: Dendreon's complete response to Item 5 was provided in BLA STN 125197/0, Amendment 017, submitted February 14, 2008. A discussion with FDA on June 13, 2008 indicated that the response to Item 5 was complete and adequate. (Refer to Type C meeting minutes submitted in Amendment 021, July 17, 2008.)

Review of supporting documentation: The purpose of this letter comment was to get a better sense whether product generated at different clinical sites was being consistently made. To address this concern Dendreon performed a statistical analysis on product lots manufactured to date at b(4) different manufacturing facilities. The statistical approach the sponsor has taken is reasonable and I consider **the sponsor's response to this review item to be acceptable.**

For Dendreon's pivotal phase III studies they used their small manufacturing facility in Seattle Washington and b(4) other contract manufacturing sites. These were located in different geographical regions in order to accommodate the complex logistics of scheduling, manufacturing, and shipping all within a short expiration period and quick manufacturing turnaround.

As can be seen in the table provided in BLA Amendment 17 the level of manufacturing at each site differed somewhat, but generally was about -b(4)- lots/site.

Table 1 Manufacturing Sites for Phase 3 Clinical Studies

Manufacturing Site, Location	Site Identification Code	Number of Lots Produced	Clinical Studies
---b(4)---------- ----------	--b(4)------	-b(4)-	D9901, D9902A, D9902B, P-11
--b(4)----------	--b(4)------	-b(4)-	D9902A, D9902B
Dendreon, Seattle, WA	4 (SEA)	-b(4)-	D9901, D9902A, D9902B, P-11
--b(4)--------- ----------	--b(4)----	-b(4)-	D9901, D9902A, D9902B, P-11
--b(4)---------- ----------	--b(4)------	-b(4)-	D9901, D9902A, D9902B, P-11

Data comparing these sites to the Morris Plains, New Jersey site were not included because this was a retrospective look at clinical lot manufacturing and at the time of the BLA original

submission the NJ plant was not producing lots for patient infusion under IND. Dendreon used a cutoff date December 31, 2005).

Approximately -b(4)- lots were used in the comparability analysis. All lots used in the study met all lot release specifications. In their evaluation Dendreon provided summary statistics on several product parameters between the different manufacturing sites. These were described in different tables and included potency as determined by the number of CD54 cells in the final product and upregulation of CD54 Dendreon did not provide an analysis of all the data sets combined, but they did provide a line listing of all the data used for their analysis and calculations based on those datasets are included in the summary table below:

[b(4)]

[b(4)]

In conducting their analysis Dendreon compared two types of data sets according to Technical Report No. 30605: Sipuleucel-T Manufacturing Site Comparability. In this study they first compared data from 2 small sets of product lots manufactured from healthy donors at the Seattle site with those of patient lots at the other b(4) clinical manufacturing sites (Healthy Donor data from Seattle Clinical Manufacturing, N = 13, and 2) Healthy Donor data from Seattle Process Development, N = 17). The 90% confidence intervals were evaluated against both the 3SD and

2SD equivalence limits established in QVD-50981, Comparability Protocol for sipuleucel-T. Equivalence Limits at 2SD were evaluated as information only in QVD-50981.

The 90% confidence intervals were also evaluated against new 2SD and 3SD equivalence limits based on two distinct sets of historical clinical data; Seattle CPC was selected based on its association to all other cell processing centers and -b(4)---------- was selected based on its status as the leading manufacturer of sipuleucel-T based on volume.

[b(4)]

Their analysis showed that each falls within 2 standard deviation Equivalence Limits .The 90% confidence interval calculated between the Seattle CPC and each of the other clinical sites falls within 2 standard deviation Equivalence Limits for the following parameters:

- --b(4)------
- ----b(4)----------
- ---b(4)----------

For comparison of the Seattle site to the -b(4)- site the 90% confidence interval falls within both the 2 standard deviation Equivalence Limits and 3 standard deviation Equivalence Limits for:

- -b(4)------
- --b(4)------
- --b(4)--------
- --b(4)--------

Dendreon concluded that the “data demonstrate that sipuleucel-T manufactured in --b(4)----------; is comparable to sipuleucel-T manufactured in the Seattle, Washington clinical facility”.

Consistent with the confidence interval analysis Dendreon performed, our own analysis and graphical representation of the same data illustrated both the high level of product variability, but also the consistency in the means and ranges between the different manufacturing sites.

[b(4)]

[b(4)]

The two plots also show that facilities that were similar in terms of the number of $CD54^+$ cells were not the most similar when evaluated in terms of CD54 upregulation (two different measures of product potency).

Note: CD54 upregulation in lots generated from the second and third apheresis tend to be significantly higher than the first infusion, but data was presented as all lots combined.

Summary of this review item: **I agree that the data sets from the different manufacturing sites demonstrate an acceptable degree of product comparability**. Product generated at each site meets lot release criteria and lots manufactured at one facility are consistent with those at other facilities.

CR ITEM #6: Additional information is needed to assess the validation of the --b(4)-------- method as an alternative sterility test method. Please address the following:

a. **For each of the datasets provided, please clarify where and when the studies were performed and the --b(4)---model that was used. We note that the ---b(4)------- Model is used in Seattle and the ----------b(4)---Model is used in New Jersey. Please discuss the differences in the two systems, including any differences in the detection algorithms. If this information is contained in another regulatory file you may submit a letter of cross-reference obtained from the manufacturer authorizing the Agency to refer to information contained in such file.**

b. **We note that you plan to "further demonstrate the suitability of the --b(4)---------- ----------" Please submit data from these additional studies.**

c. **If you intend to use the -b(4)---------- method to test sterility of -b(4)-----, please submit data to demonstrate that the -b(4)------- formulation does not have any bacteriostatic and fungistatic effects in this method.**

Sponsor's official response: A list of related submissions is provided in Table 4, including one additional study that used a wider range of microorganisms to compare the ---b(4)----- method with the CFR sterility method.

Table 4 BLA Amendments Related to --b(4)-------- Sterility Method

Amendment Number	Date	Topics
027	Apr. 16, 2009	• Results from additional direct comparison (--b(4)---------- is equivalent to CFR method)
021	Jul. 17, 2008	Dendreon minutes of June 13, 2008 teleconference • Summary table of --b(4)-------- studies • Summary tables comparing --b(4)-------- and CFR methods • Summary table of --b(4)-------- studies • Summary tables comparing --b(4)-------- and CFR methods • Summary table of --b(4)-------- studies • Summary tables comparing --b(4)-------- and CFR methods
017	Feb. 14, 2008	Response to Item 6: • Added information on sterility method datasets • --b(4)-------- manufacturer's information on models • Data on environmental isolates • --b(4)-------- not to be used for --b(4)-------- sterility testing
006	Mar. 13, 2007	• Original evaluation of the equivalence between --b(4)-------- and CFR methods

Review of supporting documentation: Dendreon clarified that for Item 6c that the -b(4)--method will not be used for sterility testing on -b(4)-- so this is not an issue. For items 6A and 6B Dendreon provided several lines of evidence that the -b(4)-------- and CFR methods are equivalent, in addition to providing the requested information about test instuments and study dates and locations. Results indicated that the --b(4)--- method is as acceptable for testing the sterility of sipuleucel-T, thus addressing the last of the Agency's concerns relating to this item.

Dendreon provided the instrument and study history information requested and conducted a larger head to head comparison of the -b(4)---- and CFR methods. The comparison of the two methods using --b(4)--------- micoroorganisms demonstrates that the two methods are equivalent. The data also support that the --b(4)---------- method -b(4)---------- detection method and that a --b(4)--------- is adequate. Therefore, the response to CR Item #6 is acceptable.

Background: Dendreon uses the ----b(4)---------- Final product sterility results for sipuleucel-T are not available at the time of product infusion. An in-process COA for infusion contains results from final product -b(4)----- and --b(4)---- in-process result.

Note: Proposed product labeling was modified at the request of the Agency to include more information to the physician on the procedures that will be used should a product lot ultimately test positive for presence of microorganisms.

At issue for the equivalency test method was that an insufficient number of organisms were evaluated. In their qualification study Dendreon only compared --*b(4)*---------- ---------- is not one of the listed test organisms in 21 CFR 610.12. --b(4)---- validation strains do include -*b(4)*-------, but is meant to be used as a substitute for -*b(4)*----------. Dendreon also did not include -*b(4)*---------- in their tests, and they did not select a second organism from the approved list of organisms. Original method validation studies that tested a wider range of microorganisms did not evaluate both sterility methods at the same time, and in some cases the time to detection by -b(4)---------- was reported as an average of several values without standard deviation. The Agency noted that the detection times with the --b(4)-------- system were reasonable, but questioned whether inoculumn levels were as low as, or lower than, those used with the CFR method.

Additional studies were performed that incorporated the recommendations of the review team. A summary of the organisms used in each of the methods is included in the table below. The cumulative results of all studies performed address this CR item.

2 Pages determined to be not releasable
b(4)

Response to item 6A:
To directly respond to CR Item 6A Dendreon provided a more detailed summary of information already presented during the original submission review (See table 1 below). For each dataset in the BLA (identified by the original data table number), they provided the testing date, location where the study was conducted, the -b(4)---------- model number and software version. An abbreviation version of that table is shown below:

Table 1: Summary of --b(4)-------- Studies

BLA Data Table Number	Test Dates (Month Year)	Dendreon Location	-b(4)------ Model	CFR Method Compared?	Inoculumn Level --b(4)------
BLA Section 3.2.S.4.3, Validation of Analytical Methods					
2	Jan 2001	SEA	--b(4)---		--b(4)---
3	Feb 2001	SEA	--b(4)---	Yes	--b(4)---
4	Feb 2001	SEA	--b(4)---	Yes	--b(4)---
5	Feb 2001	SEA	--b(4)---	Yes	--b(4)---
8	Dec 2002 to Jan 2003	SEA	--b(4)---		--b(4)---
9	Jan 2003	SEA	--b(4)---		--b(4)---
10	Nov to Dec 2003	SEA	--b(4)---		--b(4)---
12	May 2005	SEA	--b(4)---		--b(4)---
13	May 2005	SEA	--b(4)---		--b(4)---
14	Jun 2005	SEA	--b(4)---		--b(4)---
15	Jun 2005	SEA	--b(4)---		--b(4)---
16	Sep 2005	SEA	--b(4)---		--b(4)---
19	Aug 2006	NJ	--b(4)---		--b(4)---
20	Aug 2006	NJ	--b(4)---		--b(4)---
21	Aug 2006	NJ	--b(4)---		--b(4)---
22	Aug 2006	NJ	--b(4)---		--b(4)---
23	Aug 2006	NJ	--b(4)---		--b(4)---

Dendreon then went on to highlight any significant differences between between --b(4)--- and ----------b(4)--- instruments. Much of this information came from --b(4)-------. Both models have been used by Dendreon during the qualification and validation of the sterility test method. Provided in the amendment was an attached letter from -b(4)----------, dated June 5, 2007. According to the manufacturer both instruments have the same intended use, use the same types of sterility ---b(4)---------- ---------- ---------- ---------- ---------- The software and computer are also different in the two instruments. In general it seems these two instruments are close enough in functionality that there should not be major differences in their ability to detect bacterial organisms. However, it cannot be ruled out that because of the differences in controllers and especially --b(4)---------- that there might not be some difference in detection sensitivity or speed. During the

June 13, 2008 telecon Dendreon stated that --b(4)---------- instrument models were very comparable and detection times are consistent to within a few hours.

The data provided in response to Item 6A provides the information that we needed on when and how the tests were conducted. **The reponse to CR Item 6A is therefore adequate.**

Response to item 6B:
In response to Item 6B Dendreon provided three sources of supporting information: 1) summary tables compiled from previous submissions showing results obtained with the -b(4)---------- models; and 2) demonstration that the -b(4)---method was suitable for detecting new environmental isolates: and 3) a new head to head comparison with b(4) organisms.

--b(4)---------- ----------

--b(4)---- ----------

Data that more directly supports the equivalency of these two methods was presented in Amendment 27 where Dendreon reported the results of QVD-51487 “Method Validation Report: Equivalence of the --b(4)--- ---------- to the 21 CFR 610.12 Test Method. This equivalence study was meant to supplement the previous equivalency study that had only involvedb(4) organisms. The design of the study is highlighted in the tables below.

2 Pages determined to be not releasable:
b(4)

----b(4)----------

---b(4)----------

Conclusions from evaluation of the equivalency study. The head to head comparison of b(4) microorganisms tested at the same inoculation level and similar incubation conditions demonstrates the ability of the --b(4)---------- detection system is equivalent or superior to the CFR method. The data also support an evaluation period of b(4) days as adequate to detect the organisms used in these studies. **This response addresses the review issue.**

Response to item 6C:

> Sponsor's official response: As documented in Amendment 17 The -b(4)--------- method is not being used for -b(4)------ final release sterility testing. If Dendreon elects to use the --b(4)------- sterility method for any aspect of --b(4)----production in the future, we will first perform bacteriostasis/fungistasis studies and make the results available for review, as appropriate.

This response addresses the review issue.

Summary of approval of --b(4)---------- test method for sipuleucel-T:
The data presented by Dendreon support the use of the --b(4)----- assay, with a -b(4)- incubation period, as an alternative to the method specified in 21 CFR 610.12 under the conditions described in the BLA. Product lot release is based on in-process sample test result from a --b(4)----------

---------- A sample of the -b(4)------- is tested by the --b(4)---------- method and ---b(4)---------- days. The in-process sample test is continued until -b(4)---- total incubation. (See CMC review memo of Original BLA Submission for more information about samples and test method). Based on the nature of the product, manufacturing process, and short dating period of sipuleucel-T, the final results from --b(4)---------- are obtained after the product has been infused into the patients.

The package insert section 5.4 "Product Safety Testing" addresses the microbiological safety testing and the plan for follow-up by Dendreon to the prescribing physician if the -b(4)-------- results obtained after product infusion indicate microbial contamination.

CR ITEM #7: Additional data or justifications are needed to support your analytical method validations. Please address the following:

a. We note that both the --b(4)---------- methods are tested in --b(4)----------. For each of these assays, please establish a maximum variability between results of -b(4)---------- samples. Please describe what procedures will be followed if the maximum variability is exceeded.

b. We note that only gram positive organisms are used for the validation of the gram stain assay. Please include gram negative organisms as part of the validation.

c. Please revalidate your --b(4)---------- method for accuracy and intermediate precision. Please include precision studies that demonstrate the ability of operators to differentiate between viable and non-viable cells.

> Sponsor's official response: Dendreon's complete response to Item 7 was provided in BLA STN 125197/0, Amendment 024, submitted October 22, 2008. A discussion with FDA on January 15, 2009 indicated that the response to Item 7 was complete and adequate. (Refer to Type C meeting minutes, submitted in Amendment 027, April 16, 2009.)

Review of supporting documentation: In Amendment 24 Dendreon provided a summary of the changes they have made to address the Agency's concerns. They also provided copies of new validation reports.

Response to item 7A:

For the -b(4)- method (-b(4)----), the assay validity criteria establish the maximum allowable variability between -b(4)---- measures of both the test material and the assay standards. The % CV between replicates of the controls must be -b(4)- The % CV between replicates of samples must be --b(4)----------." The reason for the -b(4)--------- specification is that for most lots of sipuleucel-T, the endotoxin level is so low that a numeric value is not determined, and therefore the % CV cannot be calculated and is reported as undefined.

Note: an examination of line listing data from the BLA confirms that in most cases the endotoxin level is very low.

These assay validity criteria were previously defined only on the --b(4)---------- Assay Report Form (FRM 60166) associated with --b(4)-----. The test method has been revised so that it specifies the assay validity criteria as well. SOP 10847 Laboratory Investigations defines the procedures to be followed if the % CV of either the sample or the controls does not meet the validity criteria.

The --b(4)---------- method (--b(4)-------) has been revised as a result of the revalidation work. As recommended in the validation report (QVD 51312), new assay validity criteria related

to allowable variability have been established. The new ---b(4)---------- calculations were calculated as follows:

[b(4)]

--b(4)----------
----------.

--b(4)---------- ----------

Response to item 7B:

The revalidation of -b(4)------, Gram Stain, was provided in re-validation study QVD 51391, Method Validation. Results from the repeated study were provided. To conduct the new validation study b(4) different microorganisms were chosen. These included both Gram negative and Gram positive organisms.

[b(4)]

---b(4)---------- ----------

---

2 Pages determined to be not releasable:
b(4)

Response to item 7C:

During review of the original validation study it became apparent that the assay was not evaluated under conditions where high numbers of -b(4)--- would be present. It was necessary then to ask the sponsor to repeat the study using a wider range of --b(4)--------- in the test samples. To conduct their studies the sponsor determined both the accuracy and the precision of the --b(4)---------- method. Previously, intermediate precision included an assessment of analyst to analyst precision and instrument to instrument precision. This was previously assessed by comparing results generated from b(4) analysts using the same sample in -b(4)------- preparations. The revalidation was conducted along similar lines. As part of the revalidation a new assay validity criteria was established.

Viability assay validity calculations were calculated as follows:

[b(4)]

--b(4)--- ----------

-b(4)-- ----------

For the revalidation they established the following criteria:

[b(4)]

----b(4)---------- ----------

--b(4)--- ----------

[b(4)]

3 Pages determined to be not releasable:
b(4)

Overall summary of 7a-c: The sponsor has made a reasonable effort to either establish new criteria, to modify their test method, and/or to re-validate the Gram stain and -b(4)---------- viability test methods. The results from these studies support that these assays are suitable for their intended purpose. **The responses to items 7a-c are adequate.**

SECTION II: CMC REVIEW OF ADDITIONAL INFORMATION PROVIDED SINCE ORIGINAL BLA SUBMISSION

A. Manufacturing Logistics

B. Dating Period

C. PA2024 Recombinant Antigen –(PAP-GM-CSF)

D. Software Used in the Making of sipuleucel-T

E. Container and Package Labels

A. Manufacturing Logistics

The manufacturing process of sipuleucel-T involves few manufacturing steps. Where the logistics of manufacturing could affect product quality is when the manufacturing facility is operating at high or full manufacturing capacity (throughput). Although many of the same constraints apply at both high and low manufacturing levels, the greater the number of patients being scheduled and product lots being manufactured, the more stress it puts on their manufacturing model, the fewer redundant resources available, and the more critical the timing and coordination of each lot being manufactured. The sponsor has developed and implemented --b(4)--- software to help manage resources and to continually monitor all phases of the manufacturing process to make sure things stay on schedule.

Dendreon points to their considerable manufacturing experience in successfully manufacturing over -b(4)----lots and treating hundreds of patients in their various clinical trials. That wealth of experience is of course highly relevant. In addition recent studies supporting their responses to CR item 4b show that they can ship the product and deliver it to infusion centers with a reasonable level of product expiry remaining.

The potential concern about logisitics when manufacturing at high capacity is with the possibility of manufacturing steps or QC testing being rushed by short time constraints or limitations in resources. Very tight manufacturing and patient scheduling could also lead to potential product handling issues at the apheresis sites and infusion centers. As the sponsor describes it “The expiration attribute of the materials involved, the complexity inherent in the transportation of the material to and from the Dendreon --b(4)---------- and the capacity in which the -b(4)-- can process APCs require very precise coordination of schedules throughout the entire process.”

Dendreon indicated in their manufacturing process overview and in the relevant SOPs the process step time associated with each stage of manufacturing. Dendreon confirmed in Amendment 43 that monitoring for adherence to these established time limits was being done and clarified how the information for each step was collected.

[b(4)]

When a defined process step time is exceeded an Exception Report is initiated. The investigation includes a review of the process validation as well as process characterization studies to evaluate data generated relative to the process step time. The available data influence the product impact assessment; if no data exists the product is terminated. If Exception Report trending identifies reoccurrences, the need to implement a CAPA plan will be evaluated.

In addition, Dendreon proposes to implement alert limits that Shop Floor Management will use to adjust the testing schedule and/or the shipping schedule to provide the maximum amount of time for laboratory testing or infusion site preparation. An Exception Report would be generated if a trend is identified for exceeded alert limits. The two additional step times include monitoring that the product is delivered within -b(4)----- of expiry and that the final product QC testing is performed within --b(4)----- of sample submission.

In summary, the logistics are complex, but there are sufficient controls to ensure product quality.

B. Dating Period

The review team clarified the dating period and holding conditions for the final product prior to infusion during the review of the BLA resubmission. The dating period is 18 hours. The dating period is defined as the time from product formulation until the time of the start of infusion. As discussed earlier in this review, the product can be held at -b(4)--- for up to --b(4)---------- ----------. The product is shipped and held in the shipping container until the time of infusion. However, product handling instructions in the package insert also allow for the product to be held at room temperature for up to 3 hours once it is removed from the insulated shipping container. Infusion must begin within 18 hours of formulation of the product. Product infusion does not have to be completed prior to expiration. The expiration time and date is printed on the primary container label and on the product disposition form. The handling instructions were modeled after instructions in clinical protocols under IND, including the pivotal D9902B phase III study.

Instructions for handling at the clinical site indicate that the product should not be removed from the shipping container until the time of infusion. Data supporting the 18 hour dating period under conditions found in the shipping container were reviewed and discussed extensively earlier in this review and in the review of the original submission. Stability data meant to support the 3+ hour room temperature handling conditions was provided in Amendment 32. To simulate product handling of the commercial product -b(4)-lots were manufactured according to SOP then held at -b(4)----------, placed in the shipping container with the pre-cooled gel packs for --b(4)----------. Samples were taken at -b(4)------- hours for 5 of b(4) lots and additionally at -b(4)------ hours for the remaining b(4) lots. Viability was maintained throughout the duration of the study. -b(4)-(out of b(4)) no longer met lot release acceptance criteria for potency at the 18 hour time point (the point at which the product was removed from the shipping container) and at -b(4)---- hours. While the data did not support a dating period beyond 18 hours, the review team determined that it was sufficient to justify the conditions described in the labeling. The review team did not feel that stability concerns were sufficient to put limitations on the clinical decisions regarding the duration of infusion in the rare event when the infusion might be slowed or interrupted.

This decision is further supported by the following information:

- Product handling instructions in the package insert are consistent with handling instructions used under IND. No new handling procedures are described in the package insert with respect to how the product is to be used once removed from the container.
- Although the stability study suggested that product potency was questionable for -b(4)- of the b(4)- lots, the efficacy data from D9902B suggests that the product is stable as handled.
- The design of the stability study did not accurately reflect how the product would be handled in actual use because it included a prolonged room temperature phase at the beginning of the study. Established process step times for the manufacturing of sipuleucel-T include a step time of no more than --b(4)--- from the time of formulation with --b(4)---------- Lactated Ringer's solution to

8 Pages determined to be not releasable:

b(4)

Software Used in the Making of sipuleucel-T

Overview of three software systems:
Dendreon uses several software packages in the production of sipuleucel-T, including -b(4)----------, Laboratory Information Management Systems, --b(4)---------- software.

----b(4)----------

Laboratory Information Management Systems (LIMS) Software. LIMS was implemented in the QC lab as QC sample management and sample tracking tool. LIMS replaced a more manual system based on Microsoft Excel spreadsheets and paper forms. LIMS was put into use as a response to to a 483 item where there was concern about how the chain of identity of samples in the QC lab was being maintained and how samples were being tracked. LIMS, in conjunction with bar code readers at each analysis workstation, both maintains the COI and keeps track of which assays have been completed or are in-process. Being an electronic system it also allows much faster information retrieval on already completed asssays and lots. LIMS was described in amendments 24, 32, and 47.

LIMS consult review: A consult review was performed by Valerie Coleman, Software Reviewer, Devices Review Branch, OBRR, CBER, for evaluation validation of the LIMS software. The review found no deficiencies and the review team agrees with this conclusion. A copy of the LIMS consult review can be found in Section III, Appendix C.

--b(4)------ is the most recent software package incorporated into the manufacturing process. According to Dendreon documents "The -b(4)---------- Application is a scheduling system, developed by Dendreon and -b(4)--, to solve this scheduling problem. --b(4)---------- 'Timely' scheduling refers to the ability to respond favorably to doctor and patient requests for specific appointment times and to respond quickly. It also means the ability to react quickly to schedule changes driven by processing or transportation issues while maintaining as much of the original schedule as possible. Schedule 'accuracy' requires the system to evaluate the various constraints and develop a schedule that works within those constraints, optimizes shop floor throughput, and identifies product/treatment issues due to expiration".

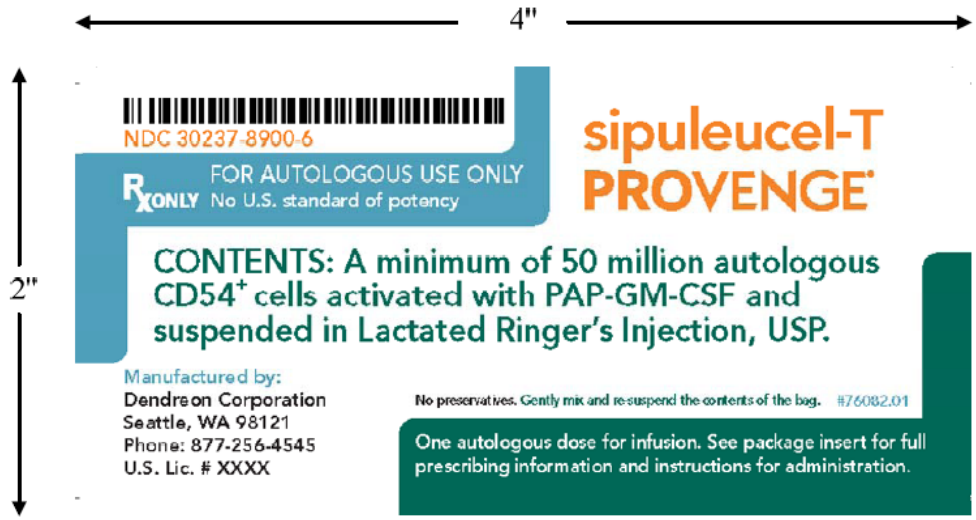
--b(4)--- consult review: A consult review was performed by Valerie Coleman, Software Reviewer, Devices Review Branch, OBRR, CBER. For review of the validation of the --b(4)------ software, additional documentation was requested from the sponsor. The materials reviewed included materials obtained during inspection, amendments 38 and 43, and information relayed by

email from the sponsor. The review team agrees that the level and type of review conducted was appropriate and agrees with the conclusions. A copy of the LIMS consult review can be found in Section III, Appendix C.

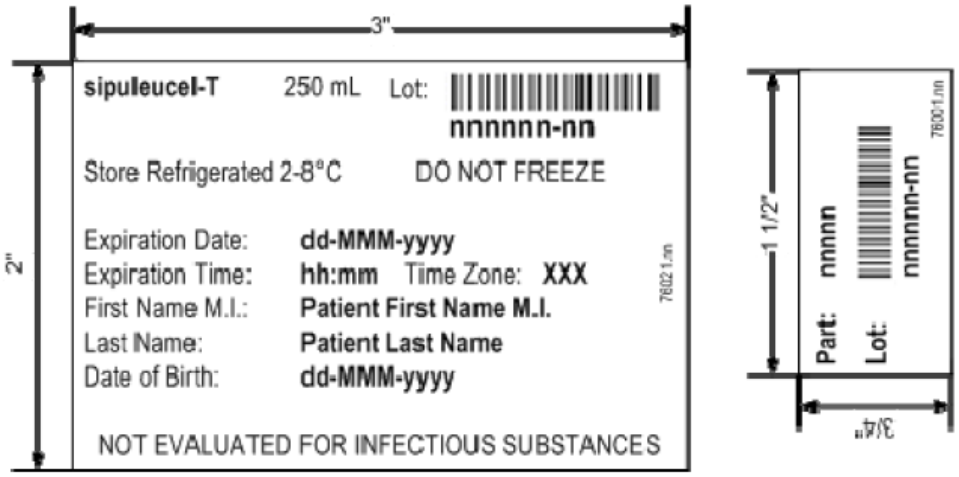
E. Container and Package Labels

Container

The infusion bag is the product container for sipuleucel-T. A sample product container (infusion bag) was submitted with affixed label as shown below. The top panel is referred to by Dendreon as the "product label". This label includes only the information that is common and relevant to all lots of sipuleucel-T.

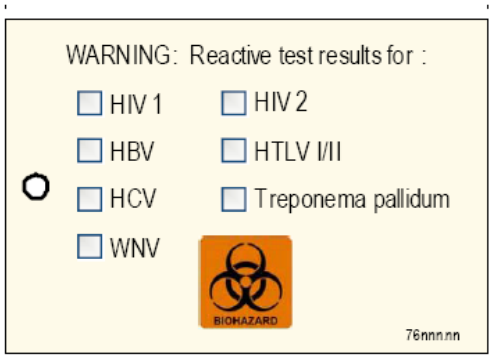


Thus this label will be identical on all containers. The bottom panel is referred to by Dendreon as the "patient specific label". This label will include lot specific information such as lot number, patient identifiers, expiration date and time.



An additional label, as shown below, will be affixed to the container only in the event that Dendreon is informed that the apheresis center policy requires testing of the autologous donor for infectious disease(s) and a positive test result was reported.

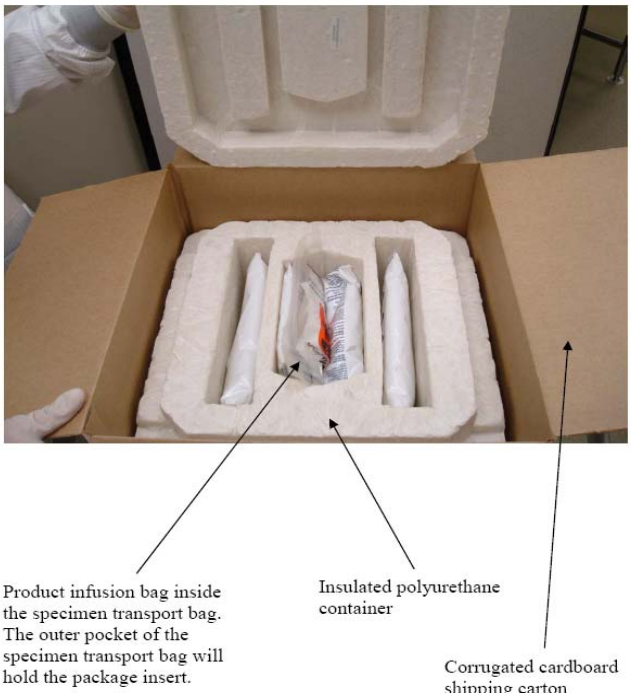
Infectious Disease Tag



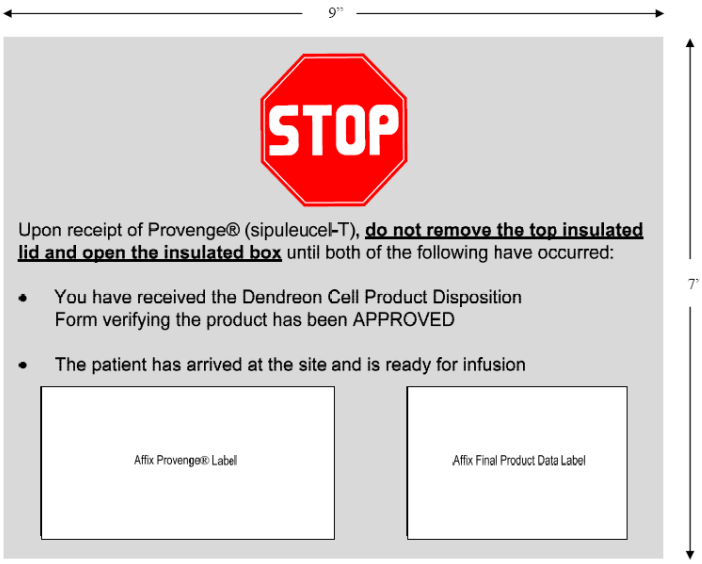
Package

For distribution and shipping, the container for sipuleucel-T is placed within a "specimen transport bag", which is a transparent bag with an adhesive seal. An outer pocket on this bag is where the product package insert will be placed.

The container within the transport bag is placed in the center compartment of an insulated polyurethane box, which is placed within a cardboard shipping carton.



The polyurethane box is the package for sipuleucel-T. The label shown below is affixed to the lid of the package. Copies of the "product" and "patient specific" labels that are affixed to the sipuleucel-T container are included on the package lid. Also included are instructions for the package handling and steps to prepare for product infusion.



For security and patient confidentiality, the cardboard shipping carton will not contain any product or patient specific label. A shipping label with the site contact name, site address, and the lot number, will be affixed to the cardboard shipping carton.

F. Post Marketing Commitment

A teleconference was held on April 15, 2010 between CMC review team members and representatives of Dendreon to discuss the CMC data and analyses that will be submitted to the BLA post licensure. Dendreon submitted Amendment 049 on April 19, 2010 to provide the following written commitment:

----b(4)--- ----------

We recommend that the approval letter to the BLA include documentation of Dendreon's commitment as stated above as post marketing commitment.

SECTION III: CMC APPENDIX ITEMS

Appendix A: List of amendments received from sponsor

Appendix B: Certificates of Analysis and Product Disposition Forms

Appendix C: Consult Review Memos for Software Validation

Appendix D: List of Definitions and Abbreviations

Appendix A: List of Amendments Received From Sponsor

Amend. No.	Date submitted	Size (pages)	Topic	CMC related	483 related
1	9/18/2006	7	Telecon minutes between Dendreon and DCGT & DMPQ about facility validation	Yes	Yes
2	11/13/2006		3.2.A appendix amendment covering System and Equipment Risk Assessment Forms	No	No
3	1/23/2007		Telecon minutes between Dendreon and CBER discussing submitting additional immune response and efficacy analyses; provided additional immune response data and updated clinical pharmacology	Yes	No
4	2/13/2007		Telecon minutes between Dendreon and DCGT regarding a possible increased risk of cerebrovascular accident (CVA) events	No	No
5	3/14/2007		Sample of draft carton label on shipping container	Yes	No
6	3/14/2007	34	Additional information provided for sterility test method equivalence, --b(4)---------- retention samples	Yes	No
7	3/20/2007		Submission of efficacy data and 4 month safety update	No	No
8	3/22/2007	18	Additional data provided on results from Moduleb(4) validation	Yes	Yes
9	4/23/2007	166	Additional clinical survival and immune response data, and supportive documentation on product manufacturing logistics, multiproduct policy, and 483 response including QC sample tracking and process step times	Yes	Yes
10	4/27/2007	15	Provides additional information on PA2024 requested in 3/15/07, 4/18/07, and 4/23/07 telecons.	Yes	No
11	5/14/2007		Statement by Dendreon that they will respond to BLA complete review letter with amendments to address CMC concerns	Yes	Yes
12	5/15/2007		Request for Type A meeting to discuss clinical requirements; proposed timing for addressing the CMC deficiencies	Yes	Yes
13	5/22/2007		Briefing document for Type A meeting to discuss clinical issues	No	No
14	8/10/2007		Request for Type C meeting to discuss CMC deficiencies	Yes	Yes
15	9/17/2007	91	Briefing document to respond to CMC-related deficiencies (items 1 - 7); Manufacturing capacity study (b(4) workstations); Planned manufacturing capacity study b(4)workstations)with b(4) lots; shipping validation plans; logistics model	Yes	Yes

16	11/6/2007	17	Provides additional comments related to campaigning commercial and clinical products in the --b(4)--------, line listing of APH shipping times to support b(4) hours dating period of starting material; line listing of shipping final product to infusion sites to support final product 18 hour shelf life; -b(4)------ manufacturers info, sterility method datasets; environmental isolates; -b(4)- not to be used for -b(4)-----	Yes	No
17	2/14/2008	175	Provides complete responses to CMC items 2 (-b(4)- shelf life), b(4) (comparability of different clinical manufacturing sites), and -b(4)---------- equivalency and validation)	Yes	No
18	2/19/2008		Request for meeting to discuss clinical issues for a BLA Amendment should the interim survival results show a positive treatment effect.	No	No
19	4/7/2008		Briefing document to discuss clinical analysis plans	No	No
20	5/19/2008		Dendreon telecon minutes from Amendment 19 telecon	No	No
21	7/21/2008	9	Dendreon telecon minutes from June 13, 2008 CMC discussion (follow-up to Amendment 17); also provides -b(4)------ summary	Yes	No
22	9/30/2008		Request for type C meeting to discuss all CR deficiencies to date and how remaining deficiencies will be addressed	Yes	Yes
23	10/14/2008		Cancellation of type C meeting	No	No
24	10/23/2008	205	Results from b(4) module b(4) workstation) process validation study with --b(4)------- lots; QC sample management; campaign manufacturing; protocol for temperature stability study; comparison of sipuleucel-T and simulated product	Yes	Yes
25	10/30/2008		Request for Type C meeting to discuss manufacturing expansion plans for NJ facility; summary of CMC responses to date	Yes	No
26	12/11/2009	25	Provides briefing document with floorplans of expansion of NJ facility; discussion of CMC responses to date	Yes	No
27	4/17/2009	269	Copy of Dendreon's telecon minutes from Type C CMC telecon of Jan. 15, 2009; line listing of product lots from D9902B and P-11 manufactured after Dec 2005; results from --b(4)---------- equivalency study	Yes	No
28	4/17/2009		Request for pre-BLA meeting to discuss clinical, statistical, and CMC issues (responses to CR letter CMC issues to date); discussion of NJ facility	Yes	Yes
29	5/7/2009	187	Briefing document for pre-BLA meeting. Provides summary of CMC responses to CR letter	Yes	Yes
30	6/4/2009	672	Updated info on PA2024 and -b(4)-	Yes	No
31	6/16/2009	28	Dendreon type C meeting minutes	Yes	Yes
32	7/30/2009	102	LIMS validation, Shipping study results; Shipping logistics data for D9902B lots manufactured in New Jersey; Room temperature stability data; update on oversight of manufacturing logistics and shop floor management	Yes	Yes
33	8/11/2009	19,000+	Clinical study reports BLA resubmission (including case report forms)	Yes	No
34	10/30/2009	10,00+	BLA resubmission (including case report forms)	Yes	Yes
35	11/16/2009	65	Clinical study reports of efficacy and safety: placebo and D9902B	No	No
36	12/23/2009	9600+	Clinical study reports of efficacy and safety: controlled and uncontrolled clinical studies	No	No

37	2/12/2010	23	Response to 2nd pre-license inspection 483 items; Logistics information for inspection lots; test results of inspection lots; production-related EM results; shipping documents and photographs	Yes	Yes
38	2/12/2010	118	-b(4)----------; final validation report for -b(4)----------; validation plan --b(4)---------- installation qualifications, -b(4)--------operational and performance qualification reports	Yes	No
39	2/18/2010	10	Additional information for production lots: process step time stamps; b(4)-- for clinical concerns.	Yes	Yes
40	2/26/2010	8	Laboratory investigation for positive Gram stain observed during inspection.	Yes	Yes
41	3/3/2010	2	Supplemental information for production lots during inspection	Yes	Yes
42	3/4/2010	105	Clinical safety and efficacy and effect of start of infusion time	Yes	No
43	3/11/2010	491	-b(4)-: process step times; QC test sample stability study; Training of physicians, apheresis sites, and infusion sites; -b(4)------description; Risk assessment for ---b(4)----------, ----------b(4)- Systems Development-b(4)-------- web portal manual	Yes	No
44	3/16/2010	2	-b(4)--- PA2024 manufacturing information	Yes	No
45	3/22/2010	9	Revised draft primary, secondary, and tertiary package labels; registry study meeting minutes	Yes	No
46	3/24/2010	8	Type C meeting request to discuss the regulatory filing strategy for the expansion of the NJ immunotherapy manufacturing facility (IMF) and licensure of -b(4)---- manufacturing facilities (multi-product)	Yes	No
47	3/29/2010	199	Remaining responses to final CMC -b(4)(facility changes not reported in BLA; -b(4)---- system; updated SOPs); Leukapheresis handbook; List of apheresis collection centers qualified by Dendreon as of May/June 2010	Yes	Yes
48	4/1/2010	6	Revised carton and product label.	Yes	No

2 Pages determined to be not releasable:
b(4)

Appendix C: Consult Review Memos for Software Validation

--b(4)----------software validation review:
Reviewed March 18, 2010.

To: File of STN 125197/0
Device: -b(4)----------
Sponsor: Dendreon Corporation
From: Valerie Coleman, Software Reviewer, Devices Review Branch
Subject: BLA Software Review Memo
Through: Linda Weir, BECS Expert, Devices Review Branch
Teresita C. Mercado, Chief, Devices Review Branch

Background:
I performed the software consult review for --b(4)---------- from Dendreon Corporation. The submission consisted of a 118 page amendment from the firm labeled, 1.6.3, Response to Request for -b(4)-------- Information. This document was in response to issues discovered during the January 25-29, 2010 FDA inspection of the firm. I received the software documentation on January 15, 2010, February 12, 2010 and February 19, 2010. Although the documents referenced two other systems: --b(4)---------- and Laboratory Information Management System (LIMS), these systems were not included as a part of the consult request from OCTGT.

Level of concern:
The software is a minor level of concern software.

Intended Use:
--b(4)---------- that is used to schedule resources used for ordering, manufacturing, and delivering sipuleucel- T and communicate planned and actual times for such activities.

Device Description:
--b(4)---------- is a scheduling tool that:

- ---b(4)--- ----------

- ---b(4)----------

- --b(4)----------

- --b(4)----------

Review Documentation-Additional Information Requested from the Firm:

Review of the submission required additional information from the firm before a recommendation could be made. FDA sent a letter requesting additional information to the firm on March 4, 2010. The firm requested a teleconference to discuss the intended use of --b(4)--------- that was held on March 5, 2010. On March 15, 2010, this reviewer received a 491 page response titled BLA STN 125197/0, Amendment No. 0043, dated March 10, 2010. The responses were adequate. The response contained a risk assessment table that identified several elements that the firm classified as a high risk priority; none of the elements appeared to be clinically significant.

Items Reviewed;

Level of concern
Intended Use
Risk Assessment
Software Description
Functional Requirements
Traceability Matrix

LIMS software validation review:

To: File of STN 125197/0
Device: Laboratory Information Management System (LIMS)
Sponsor: Dendreon Corporation
From: Valerie Coleman, Software Reviewer, Devices Review Branch
Subject: BLA Software Review Memo
Through: Linda Weir, BECS Expert, Devices Review Branch
Teresita C. Mercado, Chief, Devices Review Branch

Background:
I performed the software consult review for Laboratory Information Management System (LIMS) from Dendreon Corporation. The submission consisted of a 100- page amendment from the firm labeled, 1.12, Amendment 32_LIMS Shipping Stability Shop Floor. This document was in response to issues discussed during CMC follow-up to the June 5, 2009 Type C Meeting and a document labeled Sipuleucel-T Test Sample Management Program.

Level of concern:
The software is a minor level of concern software.

Intended Use:
The LIMS system meets good manufacturing practices (GMP) requirements by providing functions such as sample tracking, user certification, full auditing, 21 CFR Part 11 compliance capabilities, reporting, sample scheduling and bar coding. Dendreon relies on the LIMS functionality to ensure that critical GMP data is audited. LIMS audit trail features use a combination of electronic records and sample tracking history. The combination of the LIMS built-in system security and the associated operating procedures ensure that only authorized users can access or modify the data.

Device Description:
Dendreon has implemented a Laboratory Information Management System (LIMS, -b(4)------, Inc.) for the management of data and test sample flow during Quality Control (QC) environmental monitoring and Sipuleucel-T release and stability testing. This system provides superior logistic tools for sample and data management, including minimizing the potential for transcription errors. The LIMS system features the following functions:

- Improved data analysis
- Data trending and reporting
- Improved ability to track and manage laboratory testing activities
- Barcode interfacing for rapid, error-free entry of chain of identity and sample identifiers, which can be used to track samples through the laboratory workflow

Items Reviewed;

- Level of concern
- Intended Use
- Summary of LIMS Validation
- Device Description
- Sipuleucel- T Test Sample Management Program
- IOQ Results for the Release and Stability Configuration Table 1

Appendix D: List of Definitions and Abbreviations

AIT: ActiveImmunoTherapy. An AIT (sipuleucel-T or Provenge®) "sample" is defined as a single lot of material which is produced from a single apheresis.The term is also used when referring generically to both active and placebo processes or samples. AIT samples include process-related EM and all process steps.

Alert Level: Concentration of viable and non-viable particulates in a controlled environment that, when exceeded, signals a potential drift from normal operating conditions.

APC: Antigen presenting cell

APC8015: sipuleucel-T, or Provenge®

Apheresis (APH): The terms "Leukapheresis" and "Apheresis" are used interchangeably in the batch record and cell processing SOPs.

---b(4)-- ----------

APS: Advanced Planning System

--b(4)---- ----------

AOR: Acceptable Operating Range

ASM: American Society for Microbiology

B/F: Bacteriostasis and Fungistasis

--b(4)-- ----------

---b(4)--- ----------

--b(4)-- ----------

--b(4)--- ----------

---b(4)----------

BR: Batch Record: The manufacturing batch record and all associated attachments, forms, print outs, electronic records, etc. that are generated or referenced for a specific lot of product. The manufacturing batch record and all associated attachments, forms, print outs, electronic records, etc. that are generated or referenced for a specific lot of product.

BSC: Biological safety cabinet

CCRB: Change Control Review Board

CD54: Intercellular adhesion molecule-1, a glycoprotein found in the immunological synapse.

CFR: Code of Federal Regulations

CFU: Colony forming units

CBC: Complete Blood Count. A test measuring blood (or a blood derivative) for concentration or percent composition of various components (e.g., Red Blood Cells, White Blood Cells, Platelets, etc). For this test method, report the following parameters as defined by each product QCSW

Co-stimulatory molecule: A molecule on the surface of, or secreted by, an antigen presenting cell that provides a stimulus required for the activation of naïve T cells, in addition to antigen.

COI: Chain Of Identity

CPRF: Cell Product Request Form.

CPS: Cell Processing Centers
---b(4)----------
CV: Coefficient of variation (standard deviation ÷ mean, expressed as a percentage)
DI: Deionized water
--b(4)----------
DNDN: Dendreon Corporation, 3005 1st Avenue, Seattle, Washington
Donor No.: A unique identifier assigned to the apheresis donor by ---b(4)----------
---b(4)----------

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--b(4)----------
Extinction Coefficient: A measure of the amount of light absorbed per unit concentration which is constant for a particular substance.
GM-CSF: human Granulocyte Macrophage Colony Stimulating Factor
Gram (+): microorganisms that retain the primary stain and appear dark purple in color.
Gram (-): microorganisms that lose stain (decolorize) and take up the counter stain, appearing pink in color.
GRAN: Granulocytes, which includes neutrophils (NE), eosinophils (EO), and basophils (BA), reported as a percentage of WBCs
GP: Gram positive
GPC: Gram positive cocci
GPR: Gram positive rods
GVR: Gram variable rods
HCT: Hematocrit
hGM-CSF: Human granulocyte-macrophage colony stimulating factor.
--b(4)--- ----------

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--b(4)-- ----------
IMF: Immunotherapy manufacturing facility (i.e., the NJ facility)
Ig: Immunoglobulin
---b(4)--- ----------

Final Product: Final product formulation of sipuleucel-T, APC Placebo or APC 8015F
----b(4)-- ----------
FP: Final Product Specification Acceptance Criteria
----b(4)--- ----------
---b(4)---------- ----------
LIMS: Laboratory information management system, which includes data analysis templates to be used in QC testing of the proposed sipuleucel-T commercial product
LOQ: Limit of Quantitation (blood counts)

Lot: Sipuleucel-T, also referred to as APC8015, is an autologous active cellular immunotherapy product designed to stimulate an immune response against prostate cancer. Sipuleucel-T consists of autologous peripheral blood mononuclear cells, including antigen presenting cells (APCs), that have been activated in vitro with a recombinant fusion protein. The recombinant fusion protein, PA2024, is composed of prostatic acid phosphatase (PAP), an antigen expressed in prostate adenocarcinoma, linked to granulocyte-macrophage colony stimulating factor (GM-CSF), an immune cell activator. Each lot of sipuleucel-T is produced from a whole apheresis component (APH) obtained from a single patient, and returned to that patient after in vitro activation. In this submission, the term "leukapheresis", for the collection of white blood cells by apheresis, is used interchangeably with "apheresis". Similarly, the apheresis component is also termed "leukapheresis component". By definition, each sipuleucel-T product is a different lot and therefore comparisons between lots cannot be made.

LPR: Leukapheresis Procedure Report.

LR: Lactated Ringer's, Injection, USP

---b(4)---------- ----------

---b(4)--- ----------

Neat: Not diluted

NOR: Normal Operating Range

---b(4)--- ----------

--b(4)-- ----------

--b(4)-- ----------

---b(4)--- ----------

PAP: Human prostatic acid phosphatase

PA2024: A recombinant fusion protein comprised of human Prostatic Acid Phosphatase (hPAP) and human granulocyte macrophage colony stimulating factor (hGM-CSF) that is --b(4)----------

---b(4)--- ----------

Particulate Matter: Mobile, randomly-sourced, extraneous substances, other than gas bubbles, that cannot be quantitated by chemical analysis due to the small amount of material that it represents and to its heterogeneous composition.

---b(4)-- ----------

----b(4)--- ----------

---b(4)- ----------

PLI: Pre-Licensce Inspection

PNS: Part Number Specification

---b(4)-- ----------

Product: Active immunotherapy product (i.e. sipuleucel-T, APC8015F, APC Placebo)

PV: Process validation
PW: Purified water
---b(4)--- ----------

QCSW: Quality Control Summary Worksheet (FRMs 60114, 60131, 60133 and 60134)
--b(4)-- ----------
--b(4)-- ----------

--b(4)----------
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--b(4)----------
SC: Separation Container.
SD: standard deviation
SEA: Dendreon, Seattle, WA manufacturing site
--b(4)--- ----------

--b(4)--- ----------

--b(4)----------
TM: Test Method
--b(4)----------
-b(4)----------
--b(4)----------
--b(4)----------
--b(4)----------
Upregulation: Increase in molecules on the cell surface, specifically ICAM-1 (CD54)
USP: United States Pharmacopoeia
Visible Particulate: Observable foreign and particulate matter
VL: Validation Limit Acceptance Criteria
WFI: Water for Injection
WBC: White Blood Cell. White Blood Cell (WBC) concentration